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BACKGROUND: Bacterial contamination is a life-threatening risk of blood transfusion, especially with platelet (PLT) transfusions. Bacterial culturing (BCU) of PLTs as well as pathogen reduction (PRT) reduce the likelihood of such contamination. The cost-effectiveness (CE) of these interventions was analyzed after the introduction of the diversion pouch during blood collection.

STUDY DESIGN AND METHODS: The balance between costs and benefits of preventing adverse events due to PLT transfusion was assessed with a mathematical decision model and Monte Carlo simulations. Model parameters were obtained from the literature and from Dutch Sanquin blood banks. The balance between costs and benefits is assessed in terms of costs per quality-adjusted life-year (QALY).

RESULTS: The costs per 100,000 PLT concentrates in the Netherlands are estimated at $3,277,032 (€2,520,794) for BCU and at $18,582,844 (€14,294,495) for PRT. In comparison to the situation without BCU and PRT, costs per QALY are estimated at $90,697 (€69,767) for BCU (95% confidence interval [CI], $18,149-$2,088,854) and at $496,674 (€382,057) for PRT (95% CI, $143,950-$8,171,133). The ratio of differences in costs and QALYs between BCU and PRT (the relative CE) is estimated at $3,596,256 (€2,766,351; 95% CI, $1,100,630-$24,756,615). Large uncertainty in sepsis complication rates and PLT recipient survival exist, causing large uncertainties in the absolute CE for both interventions.

CONCLUSIONS: As a result of the unknown probability of sepsis complications and PLT recipient survival, the CE ratios of BCU and PRT in the Dutch setting are highly uncertain. Despite these large uncertainties, it can be concluded that BCU is without doubt more cost-effective than PRT.

With the progression of technologies, the risks of blood transfusions have been reduced considerably over the past few decades.[1] In the 1980s the risk of viral infection by blood transfusion exceeded 1 in a 1000 transfusions; nowadays this risk is more than a thousand times lower.[2] For labile blood products, the focus of prevention for viral transmission was on blood screening techniques. This approach was highly successful, but leaves residual risks that are presently primarily determined by bacterial sepsis acquired through contaminated platelets (PLTs).[2-4] Several techniques are available to prevent bacterial contamination from blood products, in particular the use of a diversion pouch, bacterial culturing (BCU) and pathogen reduction (PRT).[5-7] In November 2001, BCU on 100 percent of PLT concentrates was introduced in the Netherlands. With BCU, aerobic and anaerobic samples of the finished pooled PLT product are kept at 35°C in coculture with storage of the buffy coat–derived PLT pools, and bacterial contamination is detected through measurement of CO_2.[5,8] In July 2004 this approach was supplemented by the introduction of a diversion pouch at blood collection. This allows separation of the first 20 to 30 mL of blood, which is most likely to be contaminated by skin flora.[6]

ABBREVIATIONS: BCU = bacterial culturing; CE = cost-effectiveness; PRT = pathogen reduction; QALY(s) = quality-adjusted life-year(s).

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Another approach for reducing bacterial risk of PLTs transfusion is PRT, which recently became available for treatment of PLT products.[7] The most developed method for photochemical inactivation of bacteria is achieved by addition of a synthetic psoralen and illumination with UVA light.[9,10] This method is considerably more expensive than BCU but offers the additional benefit of reducing viral residual risks. The Dutch Health Council recently advised awaiting the results of more clinical studies, in particular on the added safety in an already safe system of blood provision, before the introduction of PRT.[11]

The Dutch Health Authorities have raised the issue of optimal versus maximal blood safety. With PRT likely to be more effective but also more costly, it may well be that—even when PRT would have maximum benefits—the balance between costs and benefits would still be unacceptable when considering the current Dutch situation with the diversion pouch. This idea is analyzed in this study, and in doing so we also assess the cost-effectiveness (CE) of the introduction of BCU: a decision that has been taken previously without an extensive evaluation of costs and benefits.

MATERIALS AND METHODS

The analysis concerns the comparison of two interventions reducing the risk of contaminated PLT transfusions (BCU and PRT) in a setting where the diversion pouch is part of standard practice and neither BCU nor PRT are introduced. We employ BCU data of 2 years of screening in the Netherlands with a diversion pouch to assess the frequency of bacterial contamination and the sensitivity of BCU. Costs and benefits are analyzed using a mathematical model that brings together data on the probability of blood contamination by bacteria and the main blood transmissible viruses: data on the consequences of contamination and data on the costs of the interventions. The analysis is performed from a direct cost perspective, which means that only the direct costs required for medical treatment are considered. There are three separate situations that are analyzed: (1) the baseline situation with diversion pouch, (2) the situation where BCU on 100 percent of the PLT products is being applied next to the use of a diversion pouch, and (3) where a PRT technique is applied next to the use of a diversion pouch. The CE of the last two alternatives is compared to the baseline situation and to each other. The latter relative CE of PRT to BCU is expressed in the ratio of differences in costs and differences in quality-adjusted life-years (QALYs) between BCU and PRT.

CE

The estimates of costs are limited to the costs of the risk reduction techniques and the direct medical costs associated with the consequences of infections. The same infections are associated with estimates of life-years lost and quality of life lost, expressed in terms of QALYs.[12] CE is expressed in terms of costs per QALY. Future costs and effects are discounted with a discount rate of 4 percent in accordance with guidelines for CE analyses.[13] Results are expressed in terms of point estimates assuming 100,000 PLT transfusions per year.

The WHO recently reported that each life-year is valued at around three times the annual earnings.[14] Therefore, an indication for a CE threshold would be three times the gross domestic product per head. For the Netherlands the threshold would be $110,000 per QALY and is comparable to the value for the United States ($120,000).

Uncertainties are addressed by uni- and multivariate sensitivity analyses. The results of the multivariate sensitivity analyses are used to calculate uncertainty margins surrounding the outcomes.

Contamination probabilities

A critical variable of the CE model is the probability of contamination. The estimated probability of an infectious PLT transfusion for viruses can be derived from the measured donor incidence rates and a virus specific window period.[15] Table 1 shows the estimated residual risk of viral contamination per PLT product for human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), and human T-lymphotropic virus-1 and -2 (HTLV-1 and -2) in the Netherlands.[16]

Hepatitis B viremia and antigen are often only transiently present in the donor blood, which leads to underestimation of the actual incidence rate. A method for estimating a correction factor for the measured incidence rate based on donation intervals is described in the literature.[17,18] On the basis of donation intervals from the Sanquin blood banks, the incidence rate was estimated to be a factor 3.0 higher than the recorded incidence rate. "PLT concentrates" in the Netherlands are prepared according to the buffy-coat method from five whole-blood donations. It should be noted that in the Netherlands only repeat donations are used for the preparation of blood products.

Since November 2001, in the Netherlands the actual bacterial contamination in PLT concentrates has been measured in 100 percent of the products. In July 2004, a diversion pouch at blood collection was also introduced. The diversion pouch separates the first 20 to 30 mL of all donations, which are most likely to be contaminated by skin flora. The risk of bacterial contamination of PLT concentrates—as presented in Table 1—is based on these measures selecting the results of 111,111 tested PLT products, collected after the introduction of the diversion pouch. As point estimate, we used a rate of 0.42 percent with an uncertainty margin of 0.32 to 0.56 percent.[20]

TABLE 1. Contamination risks of PLT blood products

Type of contamination (A)	Mean incidence among repeat donors 1997-2003[16] (per million donor years) (B)	Detection window[19] (days) (C)	Window risk (D = C/365)	Probability of infected donation in the Netherlands (per million) (E = B × D)	Probability of infected pooled (n = 5) PLT transfusion in the Netherlands (per million) (F = 5 × E)
HIV viral infection	5.5	11	0.03	0.2	0.8
HBV viral infection*	32 (11)	59	0.16	5	26
HCV viral Infection	2.6	10	0.03	0.1	0.4
HTLV-I/II viral Infection	1.5	51	0.14	0.2	1.0
Bacterial contamination of PLTs					3700

* Adjusted for nondetection. (The actual measured incidence rate is given in parentheses.)

Over the years 1998 to 2001 the Sanquin Blood Supply Foundation received on average reports of one HBV infection and five complications from bacterial contamination per year resulting from hemovigilance reported by Dutch hospitals. Because underreporting is likely, the reported incidents in combination with the annual number of PLT transfusions in the Netherlands (50,000) are used to estimate the lower bounds of the complication rates used in our model.

Consequences of contaminated donor blood

Complications of transfusion can arise immediately after the transfusion, in the case of a bacterial contamination, or at a later stage, in the case of a transmission of a chronic viral infection. A bacterial contamination becomes clinically apparent as sepsis. Although the literature offers various estimates of the incidence of sepsis, no reliable data are available on the likelihood of sepsis after transfusion of contaminated PLTs.[2,21-26] Only recently an was article published where an estimate was given for the probability of sepsis from contaminated PLT transfusions ranges from 1 in 10 to 2 in 5 (10-40%).[27] We used a point estimate of 10 percent and applied a wide margin of 1 to 40 percent to express the uncertainty surrounding this estimate. The lower limit of 1 percent represents the probability at which the model predicts the five cases of sepsis as reported by hemovigilance in the past. The upper limit (40%) equals the upper limit from the range estimate for the probability of sepsis from contaminated PLT transfusions but also corresponds to the percentage of contaminated transfused pooled PLTs that did not cause clinical complications in clinical practice (44%).[8,27] The uncertainty of the estimation was modeled with a Weibull distribution.[28] When considering bacterial sepsis, the literature reports a total of 22 deaths in 118 cases, resulting in a case-fatality rate of 19 percent.[23-26] We applied a beta distribution based on these figures to express its uncertainty.[28]

The consequences of transmitted viral infections are difficult to estimate because most viral infections have a variable, host-dependent prognosis. Several articles dealt with this issue by models on transmitted chronic viral infections.[29-35] In our model we made the conservative assumption that viral contamination will lead to transmission, cause disease, and bring about associated costs and loss of health. Even though this is a worst-case scenario, it is in line with the thought that we assess maximum benefits from PRT.

Effectiveness of interventions considered

Validation tests of the BCU system indicated a high sensitivity, defined as the proportion of contaminated products that are actually identified as being contaminated.[36,37] Its use in a production environment under a wide spectrum of bacterial contaminations might show less favorable results, as was illustrated by recent experience from routine practice in the Netherlands.[8] In routine practice 56 percent of 184 contaminated PLT products (mainly diphtheroid rods) were found to be transfused before detection by the culturing system. Even though none of these products led to complications, two nondetected contaminated PLT products led to severe septic incidents.[8] The rate of nondetected contamination of PLTs resulting in sepsis events is therefore 1 percent. Because the actual amount of unobserved contaminated PLTs is unknown and only those detected through the hemovigilance system are accounted for, in our model we allowed for a factor of 10 for underreporting of septic incidents or detection of contaminated products. We therefore modeled a sensitivity of the BCU system of 90 percent, with an uncertainty range of 9 percent.

PRT has demonstrated the reduction of contamination with at least a log 4 factor for a wide range of bacteria, viruses, and parasites.[7] PRT, however, has shown to fail reduction of bacteria in PLT concentrates as well.[38] Corresponding with the idea that we will analyze the CE of PRT at its best, we presumed the sensitivity of PRT to be 100 percent, an extreme assumption in favor of the PRT treatment.

Costs and effects

The cost estimates per PLT concentrate for BCU and PRT are presented in Table 2. Costs associated with BCU have been derived from operational data of the Sanquin blood banks. The operational costs for PRT were estimated by Sanquin and were based on the price as indicated by the manufacturer ($100 per pooled PLT concentrate; all costs were converted at a rate of 1.3 US$ per Euro). The cost of personnel, housing, and maintenance for PRT production are estimated at $19 per product. In addition, the cost of production loss due to the limited shelf life (19.8% at 5 days' outdating,[39] which is current practice), the production loss caused by the PRT process itself (10%), and the increased PLT usage in clinical practice (ranging from 0 to 30%) was accounted for.[10,40] All costs reflect costs in the year 2002.

On the basis of national hospital records the mean costs of sepsis incidents have been calculated to be $7000 per incident.[41] An estimate of the upper limit to the cost of sepsis of $18,000 was derived considering all costs of all events where sepsis was diagnosed. Based on these figures, we estimate the direct costs of sepsis treatment at $12,500 with an uncertainty margin of $7000 to $18,000.

The costs of treatment of viral diseases require longer time horizons and depend on patient prognosis. In a recent publication, estimates of the annual cost of viral diseases ranged from $1,000 to $50,000 per year depending on the type of infection.[33] An earlier CE study on PLT use indicated a maximum discounted cumulative lifetime cost of $150,000 (1996 US dollars).[31] Given the annual figures, this might seem low, but periods of high costs are accompanied with high mortality rates. These costs are also likely to occur in the remote future where discounting leads to lower values.

In our model we made the assumption that the discounted total lifetime cost of a viral infection would be $250,000, irrespective of the type of viral disease transmitted and age of the infected patient. We used a range of $125,000 to $375,000 to express our uncertainties.

In the Netherlands, PLT recipients are on average 50 years of age.[42] Patient survival is paramount in determining the CE, especially when the life expectancy is low as is the case with PLT recipients. The literature indicates that the 5-year survival of PLTs is only 21 percent.[43] We calculated the life expectancy of PLT recipients on basis of the results from Wallis and coworkers[42-44] and extended the life expectancy on the basis of our national health statistics and in accordance with the age distribution on the Dutch PLT recipient distribution. Data from the EuroQol group indicate that the average 50-year-old person has a quality-of-life index of approximately 0.75, decreasing to a value of approximately 0.65 at the age of 85.[45] Using these figures, the expected discounted number of QALYs of a Dutch PLT recipient is estimated at 4.4 years, ranging between 2 and 6 years. This estimate is used for the number of life-years lost in case a patient obtains an infection and dies from sepsis.

From other CE studies it was derived that the reduction of cumulative QALY due to viral infections is less than 5 percent.[31,33] Therefore we presumed the utility of patient obtaining a viral infection to be 95 percent (ranging between 90 and 100%).

Sensitivity analysis

On the basis of the assumptions as outlined above, event trees were constructed describing incidents and outcomes after blood transfusion for both treatment alternatives and the reference situation (no additional

TABLE 2. Model and range parameters

Description	Parameter value	Range	Distribution type
Median recipient age (years)	50	0-90	Dutch PLT
Mean QALYs	4	2-6	recipient
Probability of bacterial contamination (%)	0.42	0.32-0.56	Beta
Probability of severe sepsis given bacterial contamination (%)	10	1-40	Weibull
Probability of death given severe sepsis (%)	19	13-27	Beta
Sensitivity (%)			
BCU	90	81-99	Pert
PRT	100		
Probability of viral infection (all infections)	3×10^{-5}	1×10^{-6}-6×10^{-5}	Beta
Cost of sepsis treatment ($)	12,500	7,000-18,000	Pert
Workup cost ($)			
BCU	31	28-35	Pert
PRT	178	152-205	Pert
Increased usage of PRT PLTs (%)	15	0-30	Uniform
Total discounted cost of treatment of patient with viral infection ($)	250,000	125,000-375,000	Pert
Utility of patient with viral infection	0.95	0.9-1.0	Pert
Discount rate (%)	4		

treatment). Additionally, uni- and multivariate sensitivity analyses were carried out to assess the robustness of the results. The univariate sensitivity shows to what extent the estimates of costs per QALY change when the underlying estimates are subsequently changed within the margins of uncertainty. We analyzed whether one might draw different conclusions when varying them within these margins. In the multivariate sensitivity analysis costs and effects are assessed when all estimates are varied at the same time drawing at random from the distributions reflecting the uncertainties (Monte Carlo simulation). Table 2 summarizes all point estimates, the associated uncertainty margins, and the distributions used in the sensitivity analyses. In the case of normal distributions, the lower and upper limits of the uncertainty margins correspond with the lower and upper 95 percent limits. In the case of Pert distributions, the lower and upper limits are the real lower and upper limits. A Pert distribution is a truncated beta distribution that is characterized by a lower limit, an upper limit, and a most likely value.[28] When the distances between the most likely value and the upper and lower limit are identical (as is the case here) the shape resembles that of a normal distribution with truncated upper and lower bounds.

RESULTS

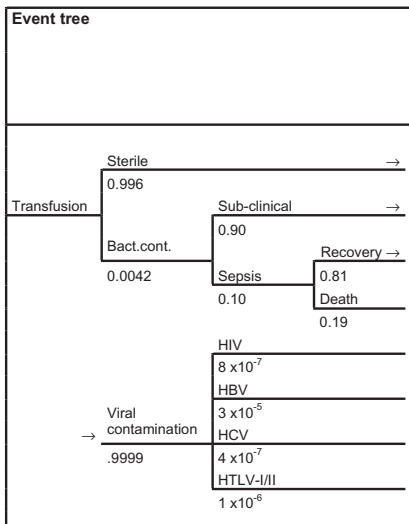
Three scenarios are analyzed after the introduction of the diversion pouch: (1) no additional treatment, (2) BCU, and (3) PRT. Figure 1 shows the event tree for the reference situation (without additional treatment) and its associated outcome probabilities together with the main outcomes of all three scenarios.

It is estimated that in 100,000 PLT transfusions BCU reduces the number of adverse events (clinical sepsis or transmission of viral diseases) from 45 to 7. In the case of perfect protection by PRT, this number would reduce it to 0. The additional costs of BCU are estimated at $3,277,032; the additional cost of PRT, at $18,582,844. This means that the cost of BCU and PRT equal $86,079 and $411,850, respectively, per event prevented. When comparing PRT with BCU, it is estimated that PRT will prevent an additional three sepsis events, one sepsis death, and three viral infections leading to a cost per additional prevented event of $2,170,959.

When associating the costs per event prevented with estimates of the QALYs lost due to these events, estimates are obtained of the cost per QALY gained. Figure 2A shows the results in terms of the relative CE of both treatments as compared to the "no additional treatment" alternative. In this graph on the vertical axis the difference in costs are plotted against the difference in QALYs on the horizontal axis. The upper cloud of points represents the outcomes of 1000 random draws from the multivariate sensitivity analysis regarding the comparison between PRT and no additional treatment. The lower cloud represents these when comparing BCU with no additional treatment. The central estimates are that BCU gains 31 (95% confidence interval [CI], 2-103) QALYs against a net cost of $2,801,202 (95% CI, $1,731,058-$3,343,982) and that PRT gains 35 (95% CI, 2-114) QALYs against a net cost of $17,349,086 (95% CI, $14,447,548-$20,420,219). For each of the situations, point estimates and 95 percent CIs are drawn in the figure. Also the CE threshold value is shown.

The costs per QALY are estimated at $90,697 (95% CI, $18,149-$2,088,854) for BCU and at $496,674 (95% CI, $143.950-$8.171.133) for PRT. Figure 2B shows the results when comparing PRT with BCU. Here differences in cost between PRT and BCU are plotted against differences in QALYs, with the same data as shown in Fig. 2A. The central estimate is a cost per QALY of $3,596,256 (95% CI, $1,100,630-$24,756,615).

In Table 3 the outcomes of the univariate sensitivity analysis are given, where it is analyzed to what extent the CE ratios of BCU versus no additional treatment and PRT versus BCU change when changing the subsequent point



Event tree	Probability (No additional treatment scenario)	Cases in 100,000 transfusions: No additional treatment	Bacterial Culturing	Pathogen Reduction
Sterile →	0.996	99,577	99,958	100,000
Sub-clinical →	0.004	381	38	0.0
Recovery →	3×10^{-4}	34	3	0.0
Death	8×10^{-5}	8	1	0.0
HIV	8×10^{-7}	0.1	0.1	0.0
HBV	3×10^{-5}	3	3	0.0
HCV	4×10^{-7}	0.04	0.04	0.0
HTLV-I/II	1×10^{-6}	0.1	0.1	0.0
Total number of events		45	7	0
Additional treatment costs ($)		0	3,277,032	18,582,844
Cost per event prevented ($)			86,079	411,850
Cost per additional event prevented ($)				2,170,959

→ means that the branch is continued at the viral contamination part of the event tree

Fig. 1. Event tree model, outcome frequencies, and costs per treatment option per 100,000 PLT transfusions.

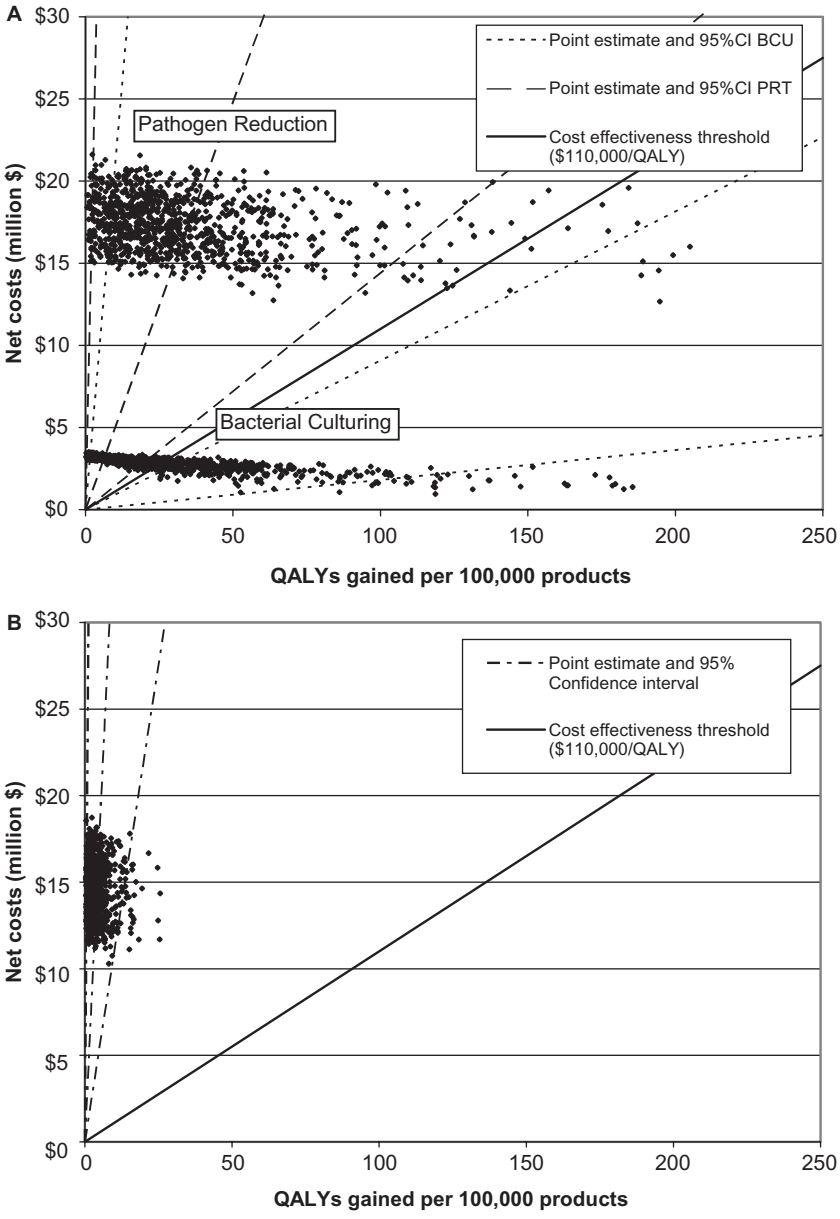


Fig. 2. (A) Relative CE of BCU and PRT versus "no additional treatment." (B) Relative CE of PRT versus BCU.

DISCUSSION

The results from this study lead to the conclusion that in the Netherlands the CE of BCU is superior to PRT. The main reason is the fact that BCU significantly reduces the incidence of sepsis events, which is the major contributor to the overall risk of PLT transfusions. Moreover, it does so against relative low costs. Although PRT may reduce this probability even further, the increase in costs are well above the costs that are considered acceptable.[14]

The main uncertainties with respect to the absolute CE concern the probability of bacterial contamination–related complications and the expected health gain. These uncertainties, however, affect both treatment options equally. So even though the absolute CE of BCU can be questioned (there is a 53% chance that it will be above the CE threshold), it will by far be more cost-effective than PRT as is shown by the relative CE graph shown in Fig. 2B. As awareness of bacterial contamination of PLTs increases and hemovigilance systems generate more data, more knowledge about the sepsis probability will become available, which will enable better estimates for the CE of these safety measures.

The modeled probabilities of sepsis (see Fig. 1; $34 + 8 = 42$ per 100,000 transfusions) and death (8 per 100,000 transfusions) through bacterial contamination are in line with values reported in literature (40-100 and 7-13 per 100,000 for sepsis and death, respectively).[24,46] It should be noted that the modeled values reflect the incidence rates after the introduction of the diversion pouch in the Netherlands, where the contamination and incident probability would be expected to be a factor two lower than the published incidence rates.[20,47] Possible other causes for differences in incidence rates might be: (1) geographic and demographic differences, (2) differences in donor collection procedures (e.g., arm cleansing), (3) the fact that the estimated sepsis probability does not reflect the Dutch setting, or (4) the reported sepsis and death incidence rates underestimate true incidence rates.

The number of sepsis events after introduction of the BCU system as predicted by the model is 1 in 24,000 transfusions. The number of sepsis events reported after the

estimates to the upper and lower limits of their uncertainty ranges (see also Fig. 3). Table 3 and Fig. 3 show that the main parameters affecting the CE are the probability of sepsis given bacterial contamination, the patients' quality-adjusted life expectancy, the probability of death given sepsis, and the probability of bacterial contamination. The model outcome is relatively insensitive to changes in all other model parameters. The table also shows that the relative CE of PRT to BCU is most sensitive to the probability of sepsis given bacterial contamination and the test sensitivity of the BCU system.

TABLE 3. Percent change in CE ratios at the outer limits of the margins of uncertainty

		Percent change					
		BCU vs. "no workup"		PRT vs. "no workup"		PRT vs. BCU	
Description	Range	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit
Probability of sepsis given bacterial contamination (%)	1-40	925	–88	703	–77	306	–72
Mean discounted quality adjusted life expectancy (years)	2-6	118	–27	118	–27	118	–27
Probability of death given severe sepsis (%)	13-27	47	–30	46	–30	38	–27
Probability of bacterial contamination (%)	0.31-0.56	38	–29	33	–25	27	–22
Workup cost PRT ($)	152-205	0	0	–16	16	–19	19
Sensitivity BCU (%)	81-99	13	–11	0	0	–43	324
Workup cost BCU ($)	28-35	–12	12	0	0	2	–2
Cost of sepsis treatment ($)	7,000-18,000	7	–7	1	–1	0	0
Probability of viral infection (all infections)	1×10^{-6}-6×10^{-5}	0	0	5	–6	20	–19
Total discounted viral infection treatment cost ($)	125,000-375,000	0	0	2	–2	2	–2
Utility of patient with viral infection (QALY)	0.9-1.0	0	0	–2	2	–13	18

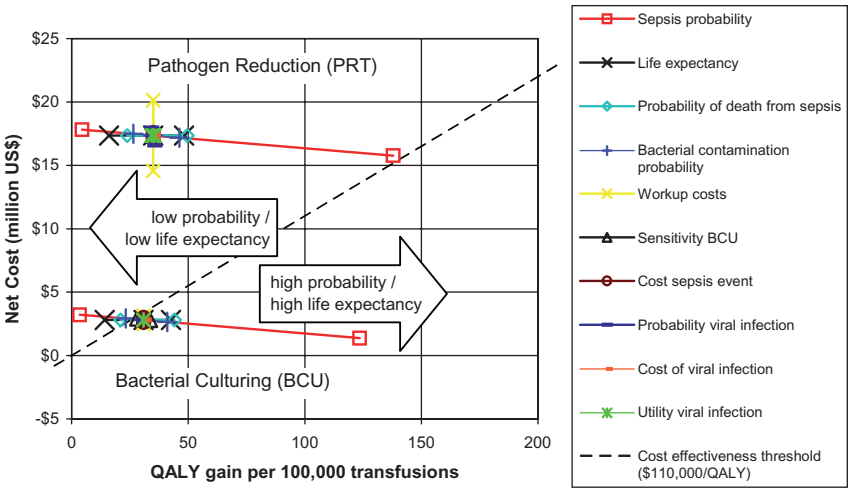


Fig. 3. Univariate sensitivity analysis of PRT and BCU. For each model parameter the CE range given in Table 2 is indicated with a line. The line markers indicate the outcomes calculated for the actual upper and lower range values. The base-case CE estimates are found in the centers of the two graph clusters. Higher complication probabilities will cause preventative measures to be more cost-effective and move the model outcome towards the cost-effective side of the graph (bottom right-hand side). This is also true in case there is much to be gained from prevention: thus for high patient life expectancy or high costs associated with complications or illness.

introduction of the BCU system, but before the introduction of the diversion pouch, was 1 in 14,000.[8] Therefore the projected number of sepsis events is about half the number of events found before the introduction of the diversion pouch and corresponds to the expected number of cases.

As a result of a high bacterial contamination probability (0.42%), there is a high number of sepsis events predicted by our model. There is a fairly large discrepancy between the number of estimated sepsis events from Fig. 1 (42 per year) and the number of sepsis events as reported by hemovigilance (5 per year). The hemovigilance reporting is likely to underestimate the true number of sepsis events because patients requiring PLT transfusions are generally severely ill and have sepsis from many other causes. Data from our academic hospital show that 10 percent of nondischarged PLT recipients will not survive one week past the date of transfusion. Even if the actual sepsis probability would be much lower than the sepsis probability modeled, however, this would result in a higher estimate for the CE ratio, but will not affect the relative CE of BCU over PRT as it will affect the benefits for both interventions.

The experience with the BacT/ALERT system in a "release as negative to date" schedule has shown that a large number of contaminated pooled PLTs (56%) are transfused before detection.[8] This shows that the system of BCU is not at all flawless. Contamination detected after delivery to the hospital, however, concerns bacteria that are slow growing and generally less pathogenic. Apparently, these do not lead to complications and the system seems to be adequately safeguarding transmission of bacterial contamination. Even though in some cases the system does fail, as shown by the cases reported back through the hemovigilance system, it remains by far a more cost-effective than PRT in preventing transmission of bacterial contamination through PLT products.

Table 3 and Fig. 3 clearly illustrate the effect of the high uncertainty with respect to the likelihood of sepsis complications on the CE of both BCU and PRT. Our analysis shows that as long as the probability of sepsis exceeds 1 in 2800 transfusions, the CE of BCU is expected to be

below the $110,000 per QALY threshold. Contrarily, there is not one variable which—within its margins of uncertainty—would lead to an estimate of the costs per QALY of PRT under $110,000 or under $1,000,000 if compared to BCU. As such, the conclusion that PRT is not very cost-effective in comparison to BCU can be called robust. The reason is that whatever assumption is made, there is little doubt that BCU is a major step forward in comparison to no additional treatment. After BCU, which reduces 90 percent or more of the bacterial contamination risk, there is barely any residual risk left. Even though PRT reduces risk completely (in our theoretical model that is), the additional effectiveness of PRT is relatively small in comparison to the additional costs.

Table 3 also shows that the relative CE is primarily influenced by the probability of sepsis given bacterial contamination and the sensitivity of BCU. This is caused by the fact that by reducing this probability the relative gain from PRT will diminish and as a result, the CE ratio will increase. An increase of the sensitivity of BCU will directly cause an increase of the relative CE ratio.

Bell and colleagues[33] estimated the CE of PRT for PLT products. Here the baseline analysis showed a CE ratio of PRT in the order of $500,000 to $2,000,000 per QALY depending on the patient type.[33] This is well in line with our point estimate of $496,674 and a 95 percent CI ($143,950-$8,171,133). In contrast to this study, we did not model any potential future scenarios. For example, long-term toxic side effects of PRT as a result of treatment were not considered, but might influence the acceptability this technology. We also did not model any effects of an unknown hepatitis C virus like agent, nor did we model any effects of an unknown nonenveloped virus that is relatively unaffected by PRT.

In our analysis we did not consider the irradiation procedure for immunosuppressed patients. We did not consider this specific subgroup as they only consume 15 percent of all PLT concentrates in the Netherlands. Possible protection against cytomegalovirus was also not assessed as 100 percent of PLTs are leukodepleted to a level less than 10^6 cells per product. The Canadian CMV consensus concluded that leukodepletion reduces CMV risk by transfusion to an undetectable level.[48]

The costs and effects associated with viral infections in our model could be considered crude or overly simplistic, especially as advanced models exist that describe disease progressions and associated costs for these diseases in detail. We applied uncertain but conservative estimates for both costs and effects, however, with respect to these diseases and found that these assumptions do not at all affect the outcome of the CE comparison of BCU and PRT, as is shown in the sensitivity analysis. Therefore, the model used is sufficiently adequate to serve its purpose.

One additional beneficial effect of BCU that is not included in our analyses is the shelf-life extension of bacterially screened PLTs. It has been shown that with BCU the PLT shelf life can be extended from 5 to 7 days, which will cause a significant reduction of the production loss.[49] Dutch data on the benefits of shelf-life extension are not available yet, but it is clear that this will further increase the CE of BCU. The cost of PRT PLTs originate primarily from the cost of the PRT process and therefore it is possible to assess the effect of extending the PLT shelf life for PRT PLTs. Our model indicates that a reduction of outdating from 20 percent to 5 percent will reduce the CE ratio of PRT by 10 percent. This will not affect any of the conclusions drawn earlier.

In the Netherlands the vast majority (86%) of PLT products are buffy coat–derived PLT pools.[16] This situation is different in the United States where the majority of PLT products are apheresis products. If costs (and methods) of PLT production in the United States would be comparable to those in the Netherlands, then BCU would be cost-effective only if the rate of sepsis through transfusion of apheresis products would exceed 1 in 3000 transfusions. As one of the reasons for applying apheresis in preparing is the reduction of the contamination rate, this is not likely to be the case.

The conclusion toward the CE of BCU is based on CE criteria applied in general health care setting where prevention or cure of disease is being judged. In case of treatment of blood products, however, the setting is different because these risks are iatrogenic. In the environmental domain the Dutch government has maintained a risk policy since the 1980s that "no individual should be exposed to an activity imposing a risk of dying greater than one in a million (10^{-6}) per year."[50] Although this standard is not applicable to the safety of medical interventions nor to blood products but for the general population, it does explicitly quantify a negligible risk level for an individual. It is clear that in the situation where no additional treatment is applied the risk of death through bacterial contamination will exceed this level, as the estimated probability of death through bacterial sepsis after BCU will be in the order of 10^{-5} per pooled PLT transfusion. Whether the introduction of bacterial screening provides a sufficient level of safety will depend on the safety level that is considered appropriate and can only be demonstrated if more insight into the incidence of transfusion-related sepsis events is obtained by hemovigilance programs. In case of treatment with PRT the required level of safety could possibly be met irrespective the sepsis incidence rate. Because no legislation with regard to acceptable contamination levels or acceptable risk of contaminations exists, here the dilemma between maximal (PRT) and optimal (BCU) risk reduction is at hand. Further research and political guidance is required to back up such decisions.

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